Preparation of Indolenines via Nucleophilic Aromatic Substitution

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Abstract: An unusual aromatic substitution to access indolenines is described. 2-(2-Methoxyphenyl)acetonitrile derivatives are reacted with various alkyl and aryl Li reagents to furnish the corresponding indolenine products, constituents of natural products, and cyanine dyes such as indocyanine green. This new method was used to synthesize 41 indolenines with large functional group tolerance, and selected examples were further converted to the corresponding indolenine dyes. Key experiments provide insight into the mechanism of this nucleophilic aromatic substitution.

DOI: https://doi.org/10.1021/acs.orglett.9b00489

Preparation of Indolenines via Nucleophilic Aromatic Substitution

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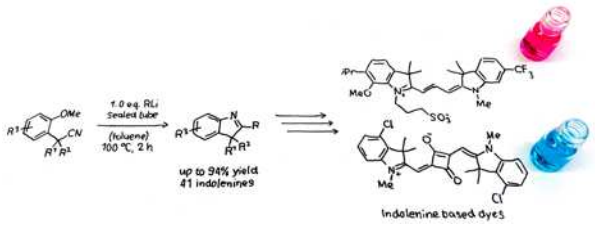
Supporting Information Placeholder

ABSTRACT: An unusual aromatic substitution to access indolenines is described. 2-(2-Methoxyphenyl)acetonitrile derivatives are reacted with various alkyl and aryl Li reagents to furnish the corresponding indolenine products, constituents of natural products and cyanine dyes such as indocyanine green. This new method was used to synthesize 41 indolenines with large functional groups tolerance and selected examples were further converted to the corresponding indolenine dyes. Key experiments provide insight into the mechanism of this nucleophilic aromatic substitution.



The indolenine or 3-*H*-indole structure can be found in many natural products (Figure 1) and is often used to access other indole derivatives such as the reduced indolines.[1] Beside their appearance in natural products and in indole synthesis, indolenines are also employed as precursors for various indolenine based dyes like indocyanine green.[2] These dyes find applications in nonlinear optics,[3] solar energy conversion,[4] imaging of diseases,[5] molecular sensors,[6] in vivo and ex vivo imaging.[7] Recently, photochromic molecules or molecular photoswitches based on an indolenine core structure received significant interest in the fields of medicine and smart materials, due to their property of changing color upon light exposure.[8] For the synthesis of the indolenine scaffold, there are numerous methods reported in the literature,[1e] which can be divided into three major groups: 1) interrupted Fischer indolization,[9] 2) dearomatization of indoles,[10] 3) intramolecular condensation of an aniline derivative with a carbonyl species to form the C-

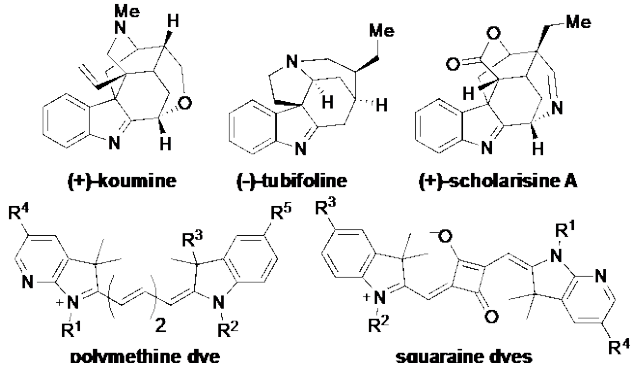
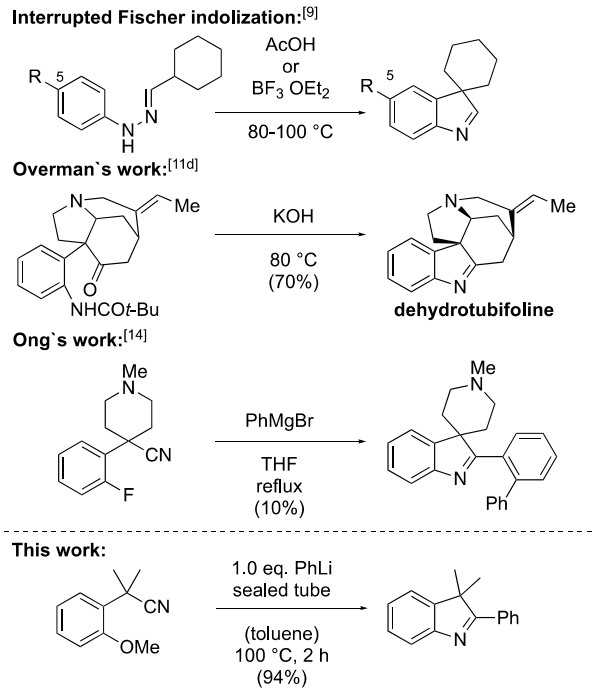


Figure 1. Indolenine-type natural products and indolenine based dyes.

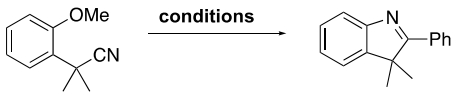
Scheme 1. Approaches towards the indolenine structure.



N bond.[11] Among the different approaches, only the Fischer indolization is used for the synthesis of indolenine based dyes, a result of the availability of the starting materials. Although this method works well for a variety of indolenines, it is limited to substituents in 5-position.[12] Otherwise, unsymmetrically substituted hydrazones result in low yields and product mixtures.[13] The group of Ong published another approach towards indolenines starting from fluoronitriles.[14] However the indolenine could only be isolated in poor yields. A similar observation

was reported by the group of Chiba, applying reductive condition to the anisol analogs with a poor yield for the indolenine.[15] During our work on benzyl nitriles, we serendipitously discovered their unique reactivity towards organolithium compounds. Upon treatment of 2-methoxyphenylacetonitrile (**1**) with phenyllihium, the formation of an indolenine was observed at higher temperatures. Intrigued by this discovery, the reaction was further optimized (Table 1). Equimolar amounts of phenyllithium gave the best results, whereas an excess of lithium reagent only lead to a lower yield for the indolenine (entry 1-3). Further optimization demonstrated that the ideal temperature is 100 °C, at which reaction is completed after 2 h (entry 7). Longer reaction times only lead to lower yields (entry 9-10). Although THF constitutes a suitable solvent, the yield is higher for toluene. Exchanging phenyllithium with phenylmagnesium bromide gave the corresponding imine and no formation of the indolenine could be observed (entry 12). Under the optimized conditions the desired indolenine **2a** was isolated in excellent 94% yield.

Table 1. Optimization for the indolenine cyclization.



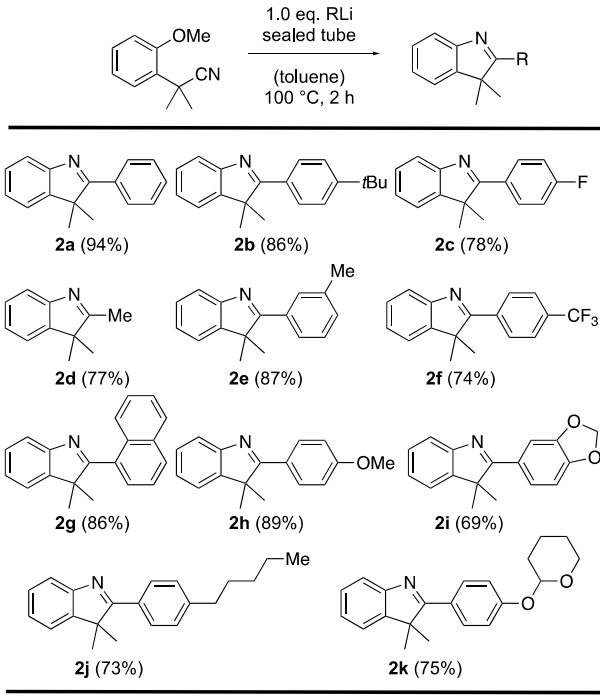
1 **2a**

entry[a]	PhLi (eq.)	T (°C)	time (h)	yield (%)[b]
1	1.2	80	1	71
2	1.5	80	1	26
3	1.0	80	1	90
4	1.0	60	1	51
5	1.0	100	1	93
6	1.0	120	1	93
7[c]	**1.0**	**100**	**2**	**94**
8[d]	1.0	100	2	90
9	1.0	100	4	91
10	1.0	100	18	92
11[e]	1.0	100	2	82
12[f]	1.0	100	2	0[g]

[a] General conditions: sealed tube, 0.3 mmol nitrile, 3.0 mL toluene. [b] yield was determined by ^{1}H-NMR with internal standard. [c] isolated yield. [d] 1 mmol scale. [e] THF as solvent. [f] PhMgBr instead of PhLi. [g] imine formation observed.

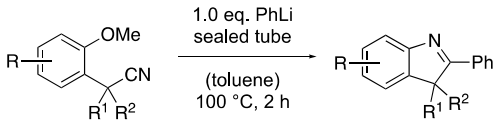
With an optimized procedure in hand, the possible modification of the organolithium reagent was investigated at first (Scheme 2). Various aryllithium reagents were employed for the cyclization giving high yields independent from donor or acceptor substituents and the substitution pattern on the aryllithium. Fluorides and a tetrahydropyran-protected phenol did not have any effect on the cyclization and gave the indolenines in high yields. Fortunately, alkyllithium reagents such as methyllithium result in indolenine formation in good yield, which are ideal precursor for the synthesis of indolenine dyes.

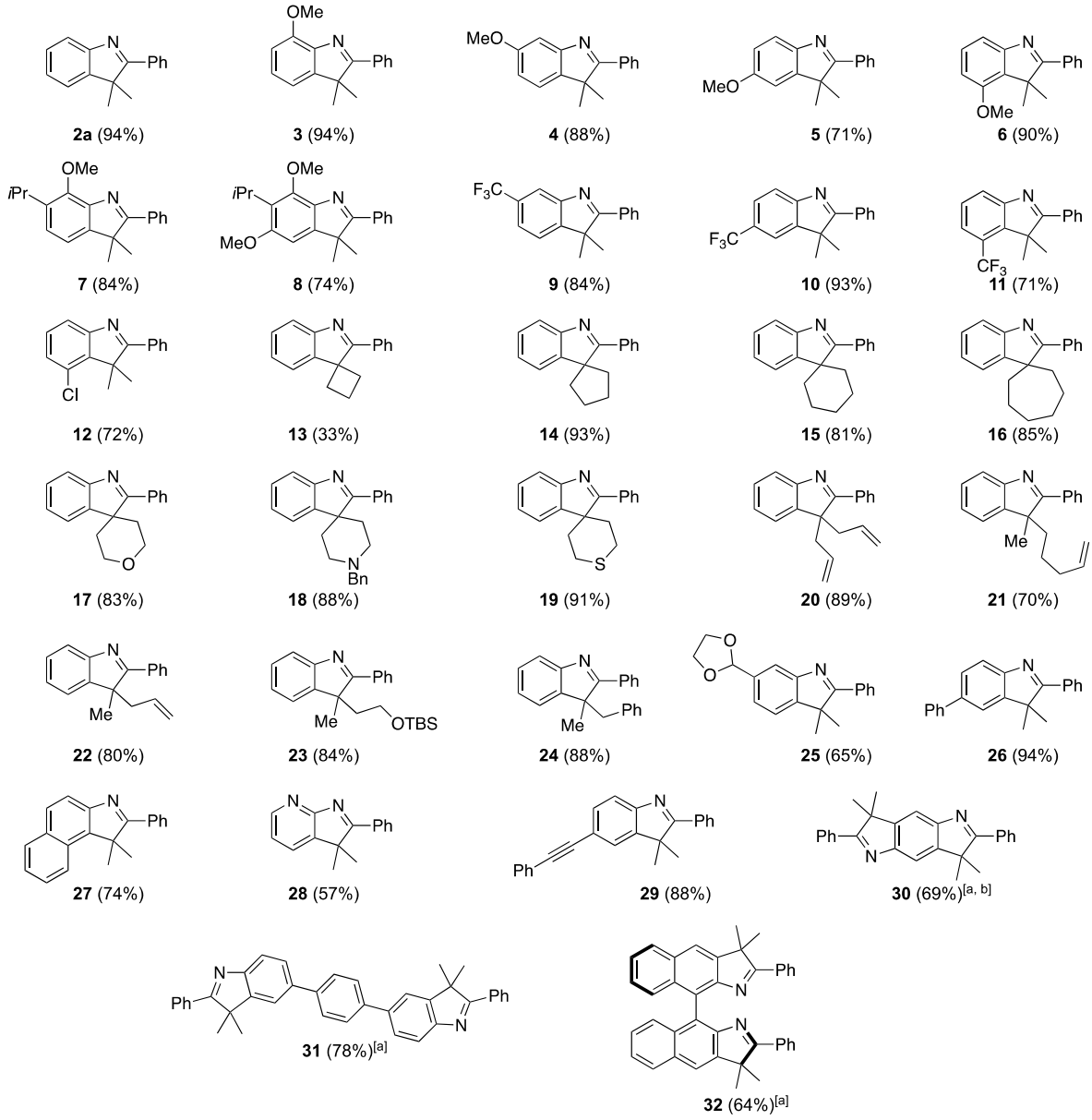
Scheme 2. Variation of the organolithium reagent.



Next the scope of the indolenine cyclization was evaluated (Scheme 3). The cyclization works well with donor substituents on the aromatic core. Furthermore, it is possible to install the methoxy substituents at every possible position on the aromatic ring in high yields. With the currently known methods, only compound **5** is accessible in good yields. As can be seen with indolenine **8,** the cyclization works well with a very electron rich benzyl nitrile, delivering a highly substituted indolenine. Beside donor substituents, electron withdrawing substituents are tolerated as well and give the corresponding indolenines in high yields. Surprisingly the cyclization method tolerates chloride substituents giving access to further modifications. Next, the benzylic position was modified with various ring sizes leading to the spiroindolenines. The 4-membered ring gave the indolenine in poor yields. All larger ring sizes delivered the cyclization product in very good yield. Oxygen-, nitrogen- and sulfur-containing rings are tolerated and give the spiroindolenines in high yields. Unsymmetric substituted nitriles showed high yields for the cyclization tolerating benzyl-, ally-groups and TBS-protected alcohols. Furthermore, various aryl-substituents, an alkyne moiety as well as an acetal-protected protected aldehyde did not affect the cyclization showing the broad application of this method. The transfer of the cyclization method to the corresponding pyridylnitriles give access to azaindolenines, which are used as precursors for near-infrared fluorescent dyes (Scheme 1).[16] Through the cyclization of various dinitriles the cyclic bisindolenines were obtained in good yields. Bisindolenine **32** was synthesized starting from (*S*)-BINOL and its use as a new ligand for metal catalysis is currently under investigation in our group.

Scheme 3. Scope of the indolenine cyclization.

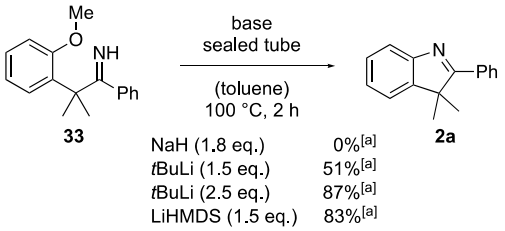




[a] 2.0 eq. PhLi [b] 4 h, 100 °C

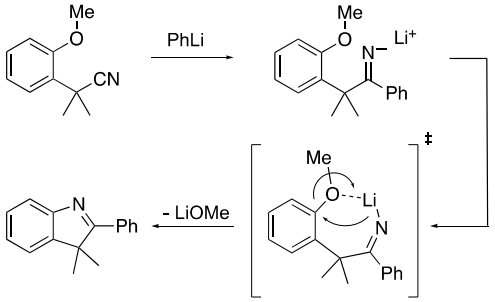
Due to the unusual reactivity of the described transformation, the mechanism of the reaction was further investigated. It is well known that nitriles react with organolithium reagents to form the corresponding imines.[17] Imine **33** as possible intermediate was treated with various bases (Scheme 4). Sodium hydride showed no formation of the indolenine. Switching from sodium hydride to the lithium base *tert*-butyllithium, a high yield for the indolenine was achieved. The weaker base LiHMDS gave similar results. This confirms the observation made during the optimization (Table 1), which underlines the crucial role of the Li counterion for the indolenine cyclization.

Scheme 4. Conversion of imine 33 to indolenine 2a with various bases.



[a] The yield was determined with ^{1}H-NMR and 1,3,5-trimethoxybenzene as internal standard

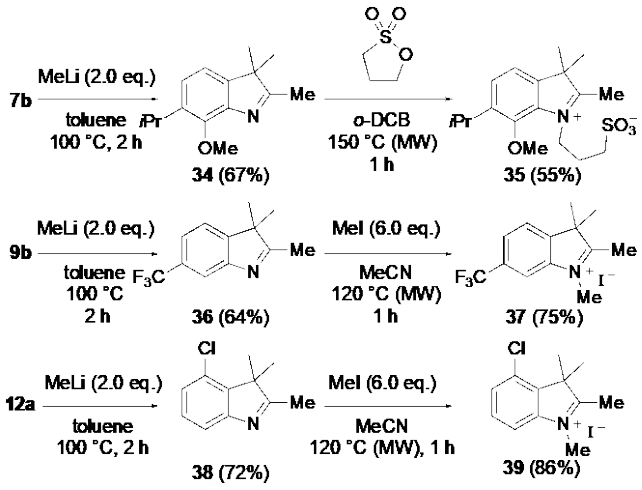
Scheme 5. Possible mechanism for the indolenine cyclization.



With these results in hand, a possible mechanism was proposed (Scheme 5). First the nitrile is attacked by phenyllithium and the intermediary imine is formed.

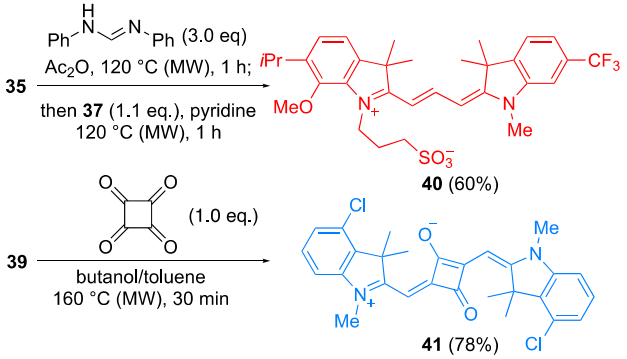
Via coordination of the lithium cation with the imine and the aromatic oxygen the methoxy group is activated as a leaving group. This activation enables the intramolecular attack of the nitrogen to the aromatic system followed by the cleavage of lithium methoxide. Other pathways via an aryne or a radical intermediate appear rather unlikely. The allylic substrates **20** and **22** both formed the indolenine in a high yield and no products resulting from a radical 5-*exo*-cyclization with the terminal double bond were observed. Furthermore, the substrates **3** and **7** with substituents ortho to the methoxy group strongly disfavor an aryne-type mechanism.

Scheme 6. Synthesis of indolenine-based salts.



o-DCB = 1,2-dichlorobenzene, MW = microwave

Scheme 7. Synthesis of indolenine-based poylmethine dye 40 and squaraine dye 41.



As mentioned before, the main advantage of the Fischer indolization is the availability of the starting materials. The nitriles required for the indolenine cyclization are accessible either in one step from the corresponding arylfluorides via a nucleophilic aromatic substitution or are already commercially available.[18]

As an application of this new method, the synthesis of indolenine-based dyes was carried out.[5b,19] Methyl indolenines **34, 36** and **38** were prepared, employing the described method in this work. The indolenines were further converted into the N-methyl iodine salts, except for indolenine **34**, which was reacted with 1,3-propanesultone to sulfonate **35** (scheme 6). The salts **35** and **37** were used to synthesize the non-symmetric purple polymethine dye **40**. Dye **40** exhibits a λ_{max} of 546 nm and due to the sulfonate moiety it is soluble in water (scheme 7). From iodine salt **39** the blue squaraine dye **41** was synthesized, which displays a λ_{max} of 632 nm. Both dyes have not been synthesized before and demonstrate the power of this new method, which allows the access to new and highly substituted indolenine based dyes. The further application of this method in the field of indolenine-based dyes is currently under investigation.

In summary, a new method for the synthesis of indolenines based on an aromatic substitution was developed. The method tolerates a variety of substituents and gives high yields independent of the position of the substituents on the aromatic ring. Further modification of the lithium reagent allows access to a broader scope of indolenines. Mechanistic investigations suggest an aromatic substitution facilitated by Li reagents. Furthermore, three indolenines were used to access new indolenine based dyes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, analytical data, ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra (PDF)

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Author Contributions

† F.H. and J.R. contributed equally equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank C. Lüthi (University of Zurich) for skillful technical assistance and the Swiss National Science Foundation for financial support (200020_163151).

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